

Hierarchical Regulation of Autophagy During Adipocyte Differentiation

Mahmoud Ahmed

Gyeongsang National University School of Medicine

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Outline

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References

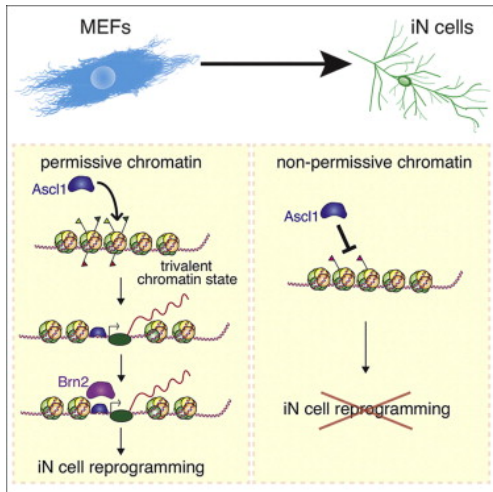
Hierarchical Regulation

Temporal (time) and spatial (site) arrangement of more than two factors regulating a set of genes.

How to evaluate the hierarchy?

1. Effect on gene expression
2. Degree of independence
3. Reliance on chromatin states
4. Types of targets they bind to

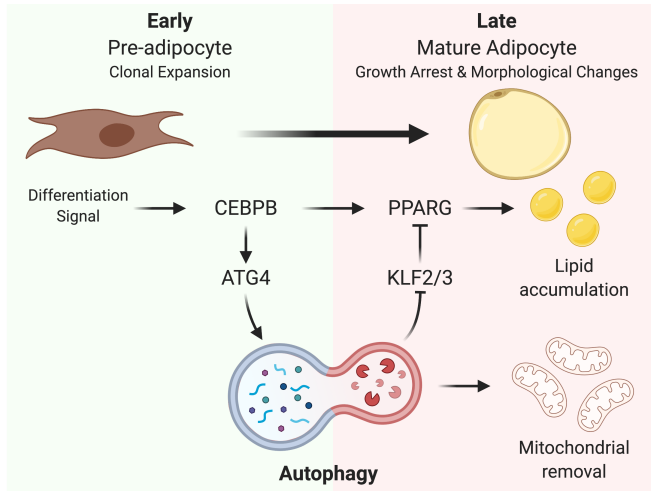
Hierarchical Mechanisms for Direct Reprogramming of Fibroblasts to Neurons



- *Ascl1* access closed chromatin to allow other factors to bind.
- *Ascl1* binds its physiologic neural targets in fibroblasts.
- A trivalent chromatin domain predicts iN reprogramming ability in other cell types.

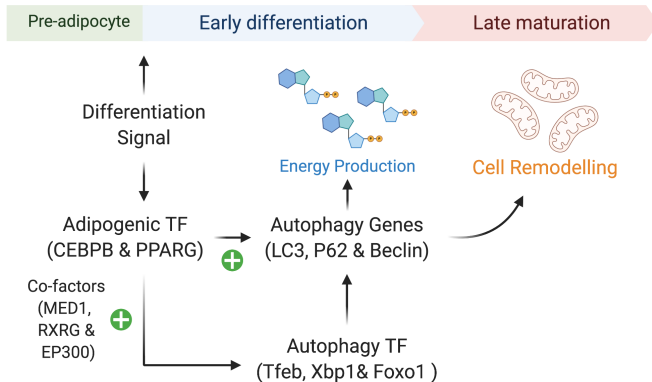
(Cell. 2013;155(3):621-35)

Contribution of autophagy in adipogenesis



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Autophagy regulation by adipogenic transcription factors



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A diagram of the study workflow

Data	Model	Output
Gene Expression	Gene Ranks	(1) Effect of binding events on gene regulation
	Regulated Groups	
Transcription Factors & co-factors binding	Peak Sets	(2) Independence from others and types of targets
	Multi-state binding model	
Histone Modifications	Multistate chromatin model	(3) Reliance on chromatin states

Methods

- Differential expression analysis
- Gene set enrichment and over-representation analyses
- Binding peak analysis
- Chromatin segmentation analysis

Datasets

Gene expression

GEO ID	N	Time (hr)	Ref.
GSE100056	2	24	[1]
GSE104508	3	192	[2]
GSE35724	3	192	[3]
GSE50612	4	0/144	[4]
GSE50934	6	0/168	[5]
GSE53244	3	0/48/240	[6]
GSE57415	4	0/4	[7]
GSE60745	12	0/24/48	[8]
GSE64757	6	168	[9]
GSE75639	3	0/48/168	[10]
GSE84410	5	0/4/48	[11]
GSE87113	5	0/2/4/48/168	[12]
GSE89621	3	240	[13]
GSE95029	8	0/48/144/192	[14]
GSE95533	10	4/0/24/48/168	[15]
GSE96764	6	0/2/4	[16]

Gene perturbation

GEO ID	N	KD	Ref.
GSE57415	8	Cebp	[7]
GSE12929	18	Pparg	[17]

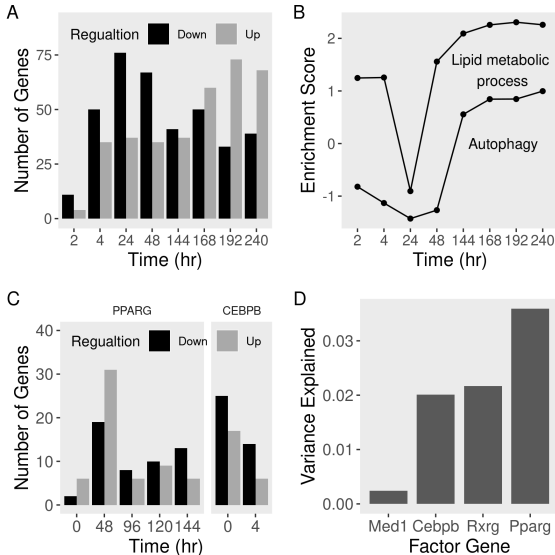
Transcription factors

SRA ID	N	Antibody	Ref.
SRP000630	12	PPARG/RXRG	[18]
SRP002337	2	PPARG	[19]
SRP002507	2	CEBPB	[20]
SRP006001	9	CEBPB/CEBPD/RXRG/PPARG	[21]
SRP028367	3	PPARG/MED1	[22]
SRP041249	3	RXRG/MED1/EP300	[23]
SRP100871	28	CTCF/MED1/NCOR1/EP300	[15]

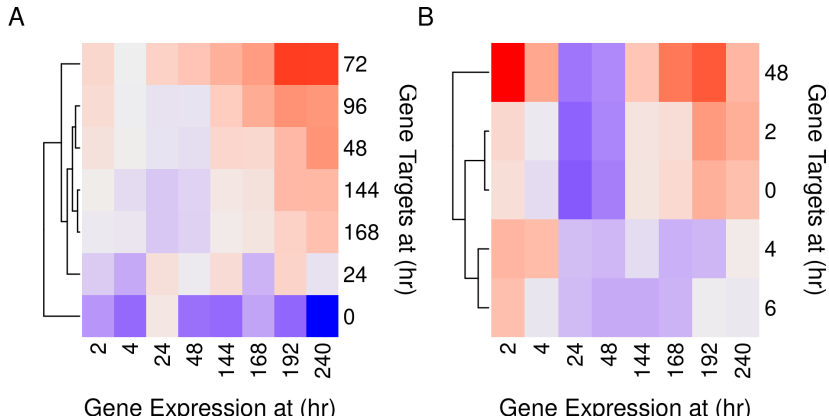
Histone modifications

SRA ID	N	Antibody	Ref.
SRP002337	11	H3K4me3/H3K27me3/H3K36me3	[19]
		H3K4me2/H3K4me1/H3K27ac	
SRP041249	6	H3K27ac/H3K4me1/H3K4me2	[23]
SRP064188	3	H3K27me3/H3K9me3	[24]
SRP078506	6	H3K4me3	[11]
SRP100871	6	H3K27ac/H3K4me1/H3K4me2	[15]

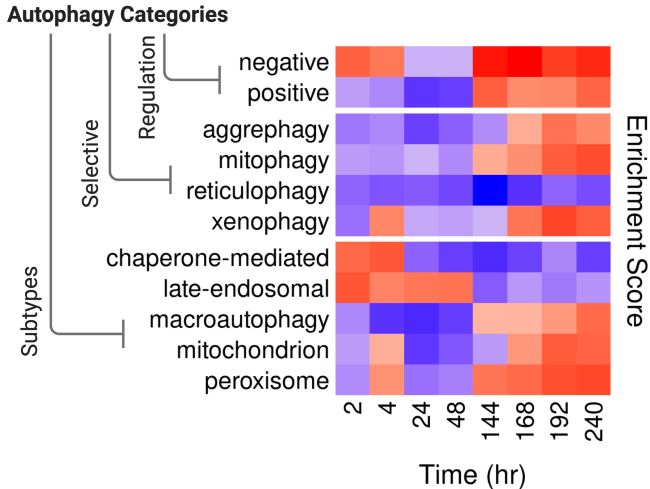
Autophagy gene products expression during adipocyte differentiation.



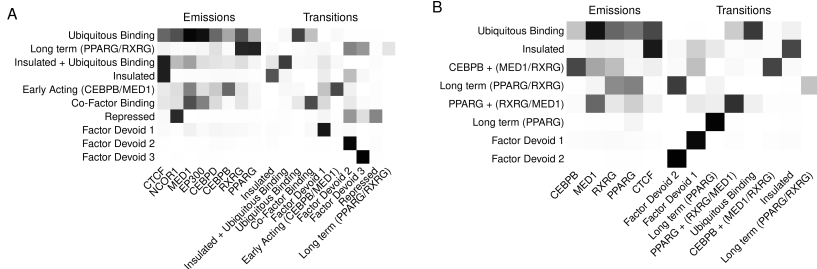
Expression of adipogenic transcription factor targets during the course of differentiation



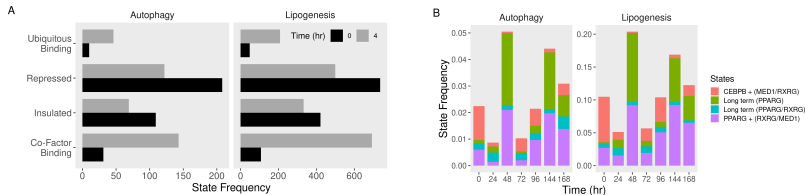
Enrichment of autophagy regulation and subtypes terms at different time points of differentiation



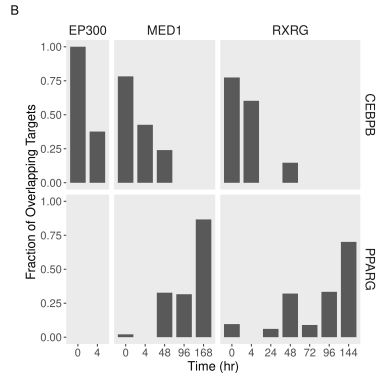
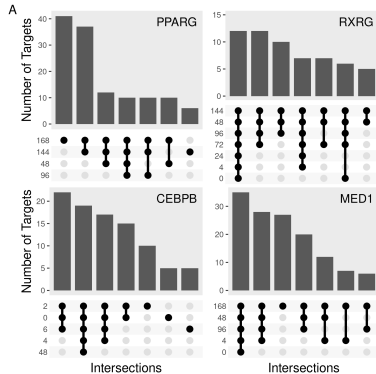
Transcription factor states in the differentiating adipocytes



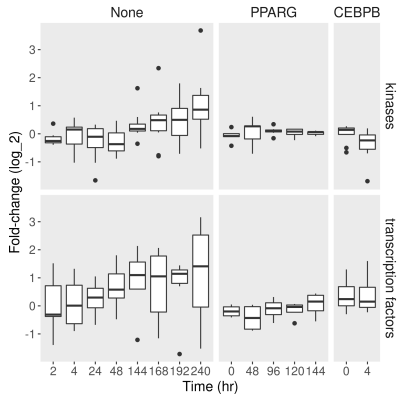
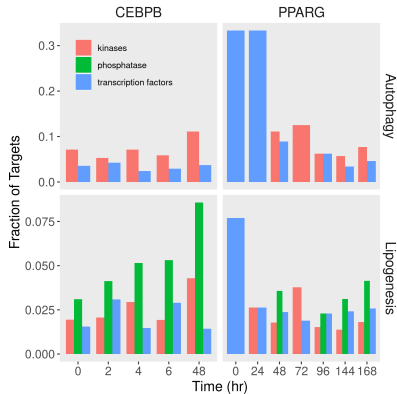
Frequencies of states in transcription factor and co-factors multi-states chromatin models



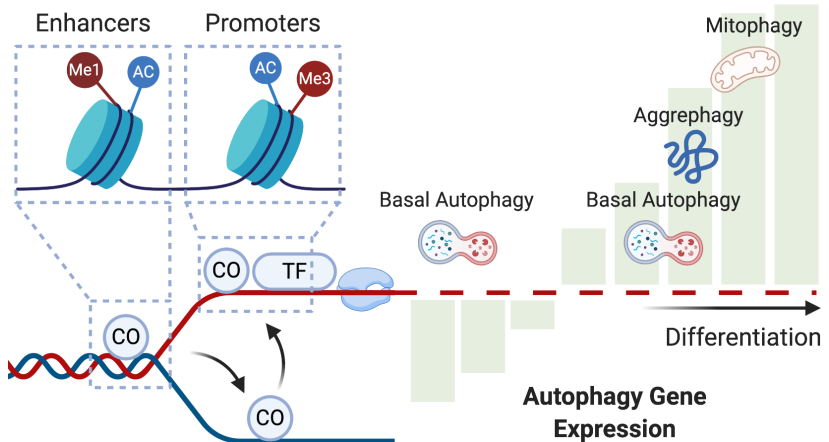
Transcription factors and co-factors targets intersect and overlap



Representation of adipogenic transcription factors targets in autophagy molecular functions



A model for transcriptional and chromatin modification on autophagy genes



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Summary

- Autophagy is regulated by adipogenic factors as a part of the adipogenesis transcriptional program.
- Co-regulators are recruited to ubiquitously bound autophagy gene regions and redistribute over time.
- Adipogenic factors are preceded by co-factors on their targets.
- Co-factors localize to and prime gene enhancers for transcription factors.
- Adipogenic factors target autophagy specific transcription factors and protein kinases.

Find out more

Mahmoud Ahmed, Trang Huyen
Lai, Trang Minh Pham, Sahib
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Hierarchical Regulation of
Autophagy During Adipocyte
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Poster number: **B-5**

Thank, *you*.

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